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Research paper

Optical resolution of *N*-(*t*-butoxycarbonyl)leucine through mixed ligand complex formation with (*R*)-*N*-(2-pyridylmethyl)pipecolatocopper(II)

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ABSTRACT

A copper(II) complex of (*R*)-*N*-(2-pyridylmethyl)pipecolate (pmpi) was prepared, and its structure was revealed by X-ray crystal structure analysis. Mixed ligand complexes were then prepared from this complex and (*R*)- and (*S*)-*N*-(*t*-butoxycarbonyl)leucinate (BocLeu). The (*R*)-BocLeu complex is less soluble in aqueous acetonitrile and more soluble in acetone than the (*S*)-BocLeu complex, and the reason was discussed on the basis of their structures. Recrystallization of the reaction mixture consisting of Cu(II) ion, pmpi, and (*RS*)-BocLeu from aqueous acetonitrile gave the (*R*)-BocLeu complex and that from acetone gave the (*S*)-BocLeu complex.

1. Introduction

Amino acids are among the most important materials for our life. Many substances for food additives, medicines, and so on are produced from amino acids. Most of optically active non-proteogenic amino acids, for instance d-amino acids, are obtained from racemic amino acids through some chemical or biochemical methods, such as optical resolution and hydrolysis of protected amino acids by enzymes or catalysts. Optical resolution is a traditional but still a common method for obtaining optically active amino acids, and some methods for optical resolutions and asymmetric syntheses using metal complexes have been reported [1–5].

Coordination around the central metal ion brings two or more molecules close to each other, and mixed ligand complexes may be considered as the site of interactions between ligand molecules [6,7]. Therefore, the structural differences between the stereoisomers may give rise to different intra- and intermolecular noncovalent interactions around the metal center and thus differences in the crystal structures and properties of complexes such as the stability and solubility. In this report, we show optical resolutions of an *N*-protected amino acids through mixed ligand complex formation by using a copper complex having an optically active ligand which is prepared easily.

2. Experimental

2.1. Materials

All chemicals were purchased from Tokyo Chemical Ind. and Wako Chemicals and used without further purification.

2.2. (R)-N-(2-Pyridylmethyl)pipecolic acid (Hpmpi)

(*R*)-Pipecolic acid (6.46 g; 50.0 mmol) was dissolved in 10 cm^3 of 5 mol/L aqueous NaOH solution and 8.20 g (50.0 mmol) of 2-chrolomethylpyridine hydrochloride was added to the resulting solution. After careful addition of 20 cm^3 of 5 mol/L aqueous NaOH solution the reaction mixture was stirred for 3 h. The resulting solution was evaporated to *ca.* 30 cm^3, and 200 cm^3 of methanol was added to the residue. The deposited salt was filtered off, and the filtrate was evaporated to dryness. The residue was washed with 100 cm^3 of ethanol to give crude sodium (*R*)-*N*-(2-pyridylmethyl)pipecolate. A hundred milliliters of water was added to the obtained sodium salt and adjusted to ca. pH 7 by 6 mol/L aqueous HCl solution. The resulting solution was evaporated to dryness, and 100 cm^3 of methanol was added to the residue. The deposited salt was filtered off, and the filtrate was evaporated to dryness, washed with water and acetone to give Hpmpi. Yield: 6.97 g (63.3%). $[\alpha]_D^{20}$ +26.8 (*c* 1.0, H_2O); mp. 150–152 °C (decomp.). ^1H NMR (400 MHz, D_2O, DSS) δ_H: 8.61 (1H, d, 6′-C*H*), 7.95 (1H, dd, 4′-C*H*), 7.58 (1H, d, 3′-C*H*), 7.52 (1H, dd, 5′-C*H*), 4.60 (1H, d, >NC*H*HAr), 4.30 (1H, d, >NCH*H*Ar), 3.60 (1H, dd, 2-C*H*), 3.52–3.40

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(1H, m, 6-C*H*H), 3.10–2.97 (1H, m, 6-CH*H*), 2.29–2.15 (1H, m, 3-C*H*H), 1.92–1.76 (3H, m, 3-CH*H*, 4-C*H*H and 5-C*H*H), 1.76–1.60 (1H, m, 5-CH*H*), 1.60–1.46 (1H, m, 4-CH*H*).

*2.3. (Acetato)((R)-N-(2-pyridylmethyl)pipecolato)(aqua)copper(II) monohydrate (**1** H_2O)*

One gram (5.0 mmol) of copper(II) acetate monohydrate dissolved in 13 cm^3 of water was added to 1.1 g of Hpmpi in 4 cm^3 of water, and the resulting solution was evaporated to dryness. The residue was dissolved in 3 cm^3 of water, and 11 cm^3 of acetone was slowly added to the solution. Standing the aqueous acetone solution at 3 °C gave blue plate crystals of **1** H_2O. Yield: 1.12 g (59%). $[\alpha]_D^{20}$ +447 (*c* 0.1, CH_3OH), mp.: 160.8–165.2 °C (decomp.).

*2.4. ((R)-N-(t-butoxycarbonyl)leucinato)((R)-N-(2-pyridylmethyl)pipecolato)(aqua) copper(II) monohydrate (**2** H_2O) and ((S)-N-(t-butoxycarbonyl)leucinato) ((R)-N-(2-pyridylmethyl) pipecolato)copper(II) (**3**)*

Complex **1** H_2O 1.09 g (2.88 mmol) was dissolved in 20 cm^3 of methanol, and (*R*)-BocLeuH 0.666 g (2.88 mmol) in 20 cm^3 of methanol was added to the solution. The resulting solution was evaporated to dryness, and the residue was recrystallized from the mixed solvent of 20 cm^3 of water and 9 cm^3 of acetonitrile. The deposited complex **2** H_2O was collected by filtration. Yield: 0.681 g (43.0%), mp. 148.2–150.8 °C (decomp.), $[\alpha]_D^{20}$ +272 (*c* 0.1, CH_3OH). Anal. Found: C; 50.17, H; 7.29, N; 7.61%. Calcd. for $C_{23}H_{39}N_3O_8Cu$: C, 50.31; H, 7.16; N, 7.65%. Complex **3** was obtained by a method similar to **2** H_2O from 0.525 g (1.39 mmol) of **1** H_2O and 0.320 g (1.38 mmol) of (*S*)-BocLeuH. Yield: 0.380 g (53.5%); mp. 103.4–108.2 °C (decomp.), $[\alpha]_D^{20}$ +139 (*c* 0.1, CH_3OH). Anal. Found: C; 53.91, H; 6.81, N; 8.20%. Calcd. for $C_{23}H_{35}N_3O_6Cu$: C, 53.84; H, 6.88; N, 8.19%.

2.5. X-Ray crystal structure analyses

The X-ray experiments for **1** H_2O, **2** H_2O, and **3** were carried out on a Rigaku RAXIS RAPID-II system with graphite-monochromated MoK α radiation (λ = 0.71075 Å). Each crystal was mounted on a nylon loop at −150 °C. For determination of the cell constant and orientation matrix, three oscillation images were taken for each frame with an oscillation angle of 3° and the exposure time of 180 s. Intensity data were collected by taking oscillation images, and the refraction data were corrected for Lorentz and polarization effects. The structures were solved by the direct method [8] and expanded by Fourier technique. Non-hydrogen atoms were refined anisotropically by full-matrix least-squares calculation. Hydrogen atoms except hydrogen atoms on C(14) and C(28) of **1** H_2O and C(17) of **3** were found on the difference Fourier map and isotropically refined. The hydrogens on C(14) and C(28) of **1** H_2O and C(17) of **3** were calculated using the riding model. All calculations were performed by using the CrystalStructure [9] and SHELXL [10] crystallographic software packages. Crystals of **3** have large vacant sites between the dimers of copper complexes, but the final difference Fourier map and the elemental analysis of crystals of **3** suggested that no crystal solvent exists in **3**. A summary of the crystallographic data and structural refinement details is given in Table 1 and interatomic distances between selected atoms are shown in Table 2.

*2.6. Optical resolution of (RS)-N-(t-butoxycarbonyl)leucine by using **1***

a) Complex **1** H_2O (0.945 g, 2.50 mmol) was dissolved in 10 cm^3 of methanol, and 1.16 g (5.02 mmol) of (*RS*)-BocLeuH in 20 cm^3 of methanol was added to the solution. The resulting solution was evaporated to dryness, and the residue was recrystallized from a solvent mixture of 15 cm^3 of water and 15 cm^3 of acetonitrile to give blue crystals of **2** H_2O. Yield: 0.205 g (14.9%). Anal. Found: C, 50.34; H, 7.18; N, 7.64%. Calcd.: C, 50.31; H, 7.16; N, 7.65%. $[\alpha]_D^{20}$ +257 (*c* 0.1, CH_3OH), mp.: 141.4–149.2 °C (decomp.).

Complex **2** H_2O thus obtained (0.205 g, 0.373 mmol) was dissolved in 60 cm^3 of water and mixed with 0.106 g (0.730 mmol) of 8-quinolinol in 15 cm^3 of acetone were mixed, and the deposited green powder was filtered off. The filtrate was evaporated to ca. 15 cm^3 and acidified to pH 2 by adding 6 mol/L aqueous HCl. The resulting aqueous solution was extracted twice with 40 cm^3 of ethyl acetate. The organic layers were combined and evaporated to dryness to give 81%*ee* of (*R*)-BocLeuH 0.057 g (10% based on a half amount of (*RS*)-BocLeuH).b) Complex **1** H_2O (0.450 g, 1.19 mmol) dissolved in 10 cm^3 of methanol and 0.551 g (2.38 mmol) of (*RS*)-BocLeuH in 10 cm^3 of methanol were mixed. The resulting solution was evaporated to dryness, and the residue was recrystallized from 3 cm^3 of acetone. The deposited blue crystals (0.359 g) were collected by filtration and dissolved in 20 cm^3 of dilute acetic acid (pH 2). (*S*)-BocLeuH was extracted from the aqueous layer with 20 cm^3 of ethyl acetate three times, and the organic layer was evaporated to dryness. Yield: 0.062 g (23% based on a half amount of (*RS*)-BocLeuH); Enantiomeric excess: 98%.

3. Results and discussion

3.1. Structures of copper(II) complexes

An optically active tridentate ligand (*R*)-*N*-(2-pyridylmethyl) pipecolic acid (Hpmpi; H denotes a dissociable proton; Scheme 1), prepared from (*R*)-pipecolic acid and 2-chloromethylpyridine, was treated with copper(II) acetate to give (acetato)((*R*)-*N*-(2-pyridylmethyl)pipecolato)(aqua)copper(II) monohydrate (**1** H_2O). Complex **1** has a distorted square-pyramidal geometry formed by two nitrogen and one oxygen atoms of pmpi, an oxygen atom of acetate, and an oxygen atom of a water molecule as shown in Fig. 1. The crystals have two stereoisomers of **1**. The oxygen atom of the C═O moiety of acetate in one of the stereoisomers seems to interact weakly with the Cu(II) ions (Cu(1)···O(4) = 2.695(3) Å) and a hydrogen atom on C-2 of the piperidine ring (3.16(4) Å). In the other stereoisomer, the carbonyl oxygen of the acetate may interact weakly with the Cu(II) ions (Cu(2)···O(9) = 2.649(3) Å) and one hydrogen atom on C-6 of the piperidine ring (2.89(4) Å). These stereoisomers interact with each other through hydrogen bonds between the coordinated oxygen atoms of acetates and the coordinated water molecules (O(5)···O(8) and O(10)···O(3)) to form an unsymmetrical dimer of complex **1**. The dimer domains interact with each other by hydrogen bonds involving the crystal waters to form the crystal structure.

The ternary copper(II) complexes consisting of pmpi and *N*-(*t*-butoxycarbonyl)leucinate (BocLeu) were prepared from **1** H_2O and (*R*)- or (*S*)-BocLeuH. The (*R*)-BocLeu complex, **2** H_2O, recrystallized from aqueous acetonitrile has a distorted square-pyramidal geometry including the carboxylate oxygen (O(3)) of (*R*)-BocLeu instead of the oxygen of acetate in **1** (Fig. 2). In a manner similar to **1**, the oxygen atom (O(4)) of the carboxylate moiety of BocLeu is located close to the copper ion with the distance of 2.7433(15) Å and one hydrogen atom on C-6 of the piperidine ring with the distance of 2.875(17) Å. The O(4) atom further interacts with the intramolecular amide NH and a crystal water molecule by hydrogen bonds (Table 2). Hydrogen-bond networks involving the coordinated and crystal water molecules may stabilize the crystal structure of **2** H_2O.

On the other hand, the (*S*)-BocLeu complex, **3**, has a distorted square-pyramidal geometry formed by tridentate pmpi, the

Table 1
Crystallographic data.

	1 H_2O	**2** H_2O	**3**
Chemical formula	$C_{14}H_{22}CuN_2O_6$	$C_{23}H_{39}CuN_3O_8$	$C_{23}H_{35}CuN_3O_6$
Formula weight	377.88	549.12	513.09
Cell system	monoclinic	orthorhombic	tetragonal
Space group	$P2_1$	$P2_12_12_1$	$P4_32_12$
a/Å	9.0226 (5)	8.8161 (4)	14.7902 (4)
b/Å	20.471 (2)	9.0762 (5)	
c/Å	9.0649 (6)	32.462 (2)	25.2140 (6)
β/°	92.584 (2)		
V/$Å^3$	1672.6 (2)	2597.5 (2)	5515.5 (3)
Z	4	4	8
D_{calc}/g cm^{-3}	1.501	1.404	1.236
F_{000}	788	1164	2168
μ/cm^{-1}	13.366	8.912	8.297
Crystal size/mm^3	0.31 × 0.13 × 0.04	0.07 × 0.06 × 0.06	0.15 × 0.12 × 0.10
Crystal color, habit	blue, plate	blue, plate	blue, block
transfer factor	0.614–0.948	0.771–0.952	0.659–0.920
No. of measured reflections	16347	25593	53939
No. of unique reflections.	7563	5963	6280
No. of variables	591	472	427
Reflections/parameter ratio	12.80	12.63	14.71
R_{int}	0.0430	0.0422	0.0629
2θmax/°	54.9	55.0	54.9
R1 value[a)]	0.0386	0.0274	0.0305
R value[b)]	0.0437	0.0319	0.0374
wR2 value[c)]	0.1004	0.0555	0.0679
p and q factors[c)]	0.0537, 0.	0.0211, 0.3903	0.0373, 0.
Goodness of fit	1.114	1.061	1.035
Min./max. peak in final difference Fourier map/e $Å^{-3}$	−1.11/0.52	−0.29/0.30	−0.21/0.23

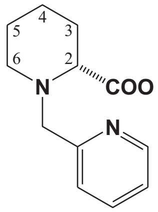
a) $R1 = \sum ||Fo| - |Fc|| / \sum |Fo|$ (for $I > 2\sigma(I)$).
b) $R = \sum ||Fo| - |Fc|| / \sum |Fo|$ (for all reflections).
c) $wR2 = [\sum (w(Fo^2 - Fc^2)^2) / \sum w(Fo^2)^2]^{1/2}$; $w^{-1} = \sigma^2(Fo^2) + (p \cdot P)^2 + q \cdot P$; $P = (Max(Fo^2,0) + 2Fc^2)/3$ (for all reflections).

Table 2
Interatomic distances between selected atoms.

Atom	Atom	Distance/Å	Atom	Atom	Distance/Å
1 H_2O					
Cu(1)	O(1)	1.958(3)	Cu(1)	O(3)	1.977(2)
Cu(1)	O(4)	2.695(3)	Cu(1)	O(5)	2.230(3)
Cu(1)	N(1)	1.998(3)	Cu(1)	N(2)	2.025(3)
Cu(2)	O(6)	1.956(3)	Cu(2)	O(8)	1.985(2)
Cu(2)	O(9)	2.649(3)	Cu(2)	O(10)	2.221(3)
Cu(2)	N(3)	2.004(3)	Cu(2)	N(4)	2.020(3)
O(2)	O(12)[a]	2.741(4)	O(3)	O(10)	2.776(4)
O(3)	C(13)	1.282(4)	O(4)	O(11)	2.745(4)
O(4)	C(13)	1.236(5)	O(5)	O(8)	2.809(5)
O(5)	O(11)[b]	2.742(5)	O(7)	O(11)[c]	2.804(4)
O(8)	C(27)	1.286(4)	O(9)	O(12)[d]	2.725(4)
O(9)	C(27)	1.246(5)	O(10)	O(12)	2.711(5)
2·H_2O					
Cu	O(1)	1.9538(12)	Cu	O(3)	1.9723(13)
Cu	O(4)	2.7433(15)	Cu	O(7)	2.2820(15)
Cu	N(1)	1.9959(14)	Cu	N(2)	2.0092(13)
O(2)	O(8)[e]	2.710(2)	O(3)	C(13)	1.278(2)
O(4)	O(8)	2.761(2)	O(4)	N(3)	2.685(2)
O(4)	C(13)	1.230(2)	O(5)	O(7)[f]	2.869(2)
O(7)	O(8)[g]	2.754(2)			
3					
Cu	O(1)	1.9449(15)	Cu	O(3)	1.9671(14)
Cu	O(4)	2.6931(13)	Cu	O(5)[h]	2.3584(14)
Cu	N(1)	2.0037(16)	Cu	N(2)	1.9985(16)
O(3)	N(3)	2.707(2)	O(3)	N(3)[h]	2.877(2)
O(3)	C(13)	1.291(2)	O(4)	C(13)	1.235(2)

Symmetry Operations: a: −x + 1, y + 1/2, −z + 1; b: x, y, z−1; c: −x, y−1/2, −z + 1; d: x, y, z−1; e: x + 1/2, −y + 1/2, −z + 1; f: x, y−1, z; g: x, y + 1, z; h: y, x, −z.

carboxylate oxygen (O(3)) of (*S*)-BocLeu, and the oxo moiety (O(5′)) of the *t*-butoxycarbonyl group on the neighboring complex (Fig. 3). In crystals, **3** forms a symmetrical dimer connected by the weak coordination (Cu–O(5)′ = 2.3593 (14) Å) and a hydrogen bond (N(3)···O(3)′ = 2.877 (3) Å) between the complex molecules instead of the hydrogen-bond networks of coordinated and crystal waters in **2** H_2O. The amide NH, which interacts with the intramolecular carbonyl oxygen atom (O(4)) of the coordinated carboxylate in **2** H_2O, forms hydrogen bonds with the two coordinated carboxylate oxygen atoms on the same (*S*)-BocLeu (O(3)) and the other one



Scheme 1. Numbering scheme of carbon atoms of pmpi.

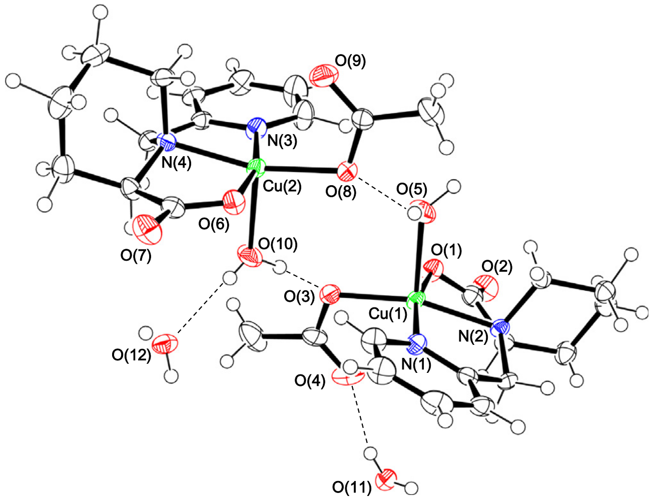


Fig. 1. ORTEP drawing of **1** H_2O.

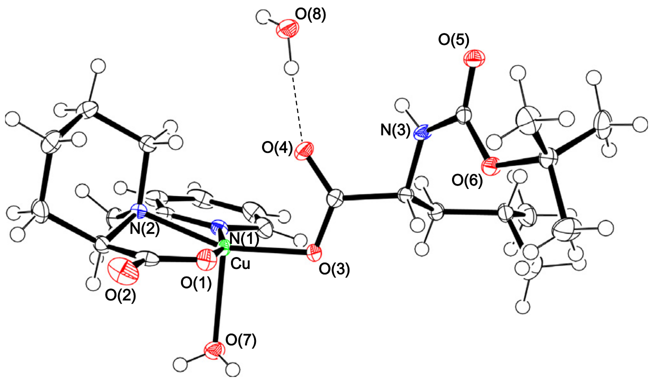


Fig. 2. ORTEP drawing of **2** H_2O.

(O(3′)) in the dimer. No significant interaction exists between the dimers of **3**.

3.2. Optical resolution of N-(t-butoxycarbonyl)leucine by using (R)-N-(2-pyridylmethyl)pipecolatocopper(II)

The differences in intermolecular interactions between the crystals of **2** H_2O and **3** influence their solubilities. Table 3 shows that **2** H_2O is about 20 times more soluble than **3** in acetone, while **3** is 3 times more soluble than **2** H_2O in aqueous acetonitrile. Complex **2** is crystallized preferentially by hydrogen bonds between coordinated water molecules, while formation of the dimeric structure of **3** takes place with coordination of the *t*-butoxycarbonyl group and interligand hydrogen bonds and requires no crystal water. Because water molecules are not provided in acetone, **2** lacks the crystal waters and is therefore unable to form the hydrogen bond network in acetone. On the other hand, the dimer formation of **3** in aqueous acetonitrile may be inhibited by coordination of a water molecule to the axial position in place of the *t*-butoxycarbonyl group and by interactions between the coordinated ligands and solvent molecules, and therefore **3** is more soluble than **2** in aqueous acetonitrile.

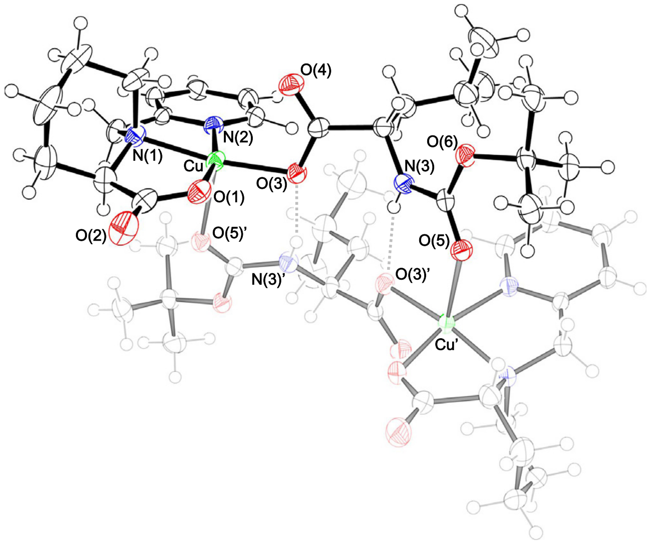


Fig. 3. ORTEP drawing of **3**.

Table 3
Solubility of Cu(II) ternary complexes.

Solvent	**2** H_2O	**3**
Acetone	2.76	0.13
H_2O - CH_3CN (1:1 v/v)	4.14	11.4

a) g/(100 g of solvent).

Optical resolution of (*RS*)-BocLeuH was attempted by using **1**. Equimolar amounts of (*RS*)-BocLeuH and **1** H_2O were mixed in methanol, and the resulting solution was evaporated to dryness to form Cu-pmpi- (*RS*)-BocLeu ternary complexes. Recrystallization of the reaction mixture from aqueous acetonitrile gave **2** H_2O as blue crystals, while recrystallization from acetone gave **3** as blue crystals. Treatment of the crystals of the ternary complexes from aqueous acetonitrile containing 74% of **2** with 8-quinolinol gave 81%*ee* of (*R*)-BocLeu, and treatment of the crystals from acetone in the same way gave 98%*ee* of (*S*)-BocLeu by extracting with ethyl acetate and dilute acetic acid.

4. Conclusion

The copper complex with (*R*)-*N*-(2-pyridylmethyl)pipecolate was prepared and employed for optical resolution of (*RS*)-BocLeuH *via* mixed ligand complex formation. The mixed ligand complex including (*R*)-BocLeu was less soluble in aqueous acetonitrile and more soluble in acetone than that including (*S*)-BocLeu. Recrystallization of the reaction mixture consisting of Cu(II) ion, pmpi, and (*RS*)-BocLeu from aqueous acetonitrile and that from acetone gave the (*R*)-BocLeu complex and the (*S*)-BocLeu complex, respectively.

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Appendix A. Supplementary material

Crystallographic data for **1**·H_2O, **2**·H_2O, and **3** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication numbers CCDC 1544766-1544768, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-003; e-mail: deposit@ccdc.cam.ac.uk; URL: http://www.ccdc.cam.ac.uk/).

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